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Serial N°: 09/896,278

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Title : New diphenylurea compounds

Art Unit : 1624

Examiner : Emily BERNHARDT

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION UNDER 37 CFR 1.132

I, Mark MILLAN, a citizen of the United Kingdom, of 19, rue du Président Wilson, 78230 LE PECQ, France, declare and say that :

I hold the degree of Bachelor of Arts (1978), Master of Arts (1983), and Doctor of Sciences (1985) from the University of Cambridge (England).

Since 1995, I have been Director of the Division of Psychopharmacology at the Institut de Recherches Servier, France.

I am the author or co-author of more than 500 international publications such as patents, scientific publications and communications.

I am one of the co-inventors of US Patent Application Serial n° 09/896,278 filed June 29, 2001 concerning "New diphenylurea compounds".

I am thoroughly familiar with the above-mentioned patent application and fully support the pharmacological data contained in application which were performed either by me or under my supervision. I also fully support the

conclusions derived and the arguments presented as concerns the therapeutic interest of the compounds described.

The compounds of the present invention have pharmacological properties which allow their use in the treatment of disorders of the central nervous system.

The following publications, enclosed with this Declaration, correlate and demonstrate the existing relation between the pharmacological activity in the different tests presented in the present application Serial n° 09/896,278, in Examples A to D and their potential in the treatment of psychiatric disorders.

Example A: Penile erection in rat induced by a 5-HT_{2c} selective agonist, RO 60-0175, is a specific method in order to demonstrate the *in-vivo* 5-HT_{2c} agonist properties of compounds checked [Berendsen, H.G., et al, Involvement of 5-HT_{1c}-receptors in drug-induced penile erections in rats, *Psychopharmacology*, **101**, 57-61 (1990); Millan, M.J., et al, 5-HT_{2c} receptors mediate penile erections in rat: actions of novel and selective agonists and antagonists, *Eur. J. Pharmacol.*, **325**, 9-12 (1997)].

Example B: Aggressive behavior in isolated mice brings to mind anxiolitic properties [Millan M.J. et al., S 33005, A novel ligand at both serotonin and norepinephrine transporters: II. Behavioral profile in comparison with venlafaxine, reboxetine, citalopram and clomipramine, *J. Pharmacol. Exp. Ther.*, **298** (2), 581-591 (2001)]. 5-HT_{2c} receptors are implied in the aggressive behavior [Shih J.C. et al., Ketanserin and tetrabenazine abolish aggression in mice lacking monoamine oxidase A, *Brain research*, **835**, 104-112 (1999)].

Example C: Marble–burying in the mouse suggests antidepressant and/or anti-impulsive properties [Millan et al., S 33005, A novel ligand at both serotonin and norepinephrine transporters: II. Behavioral profile in comparison with venlafaxine, reboxetine, citalopram and clomipramine, *J.*

Pharmacol. Exp. Ther., **298** (2), 581-591 (2001)]. 5-HT_{2c} receptors play a part in the aggressive behavior expression [Koskinen T. et al., The 5-HT_2 receptor activation enhances impulsive responding without increasing motor activity in rats. *Pharmacol. Biochem. Behav.*, **66** (4), 729-738 (2000)].

Moreover as it was mentioned in the present Application Serial n° 09/896,278 (page 2) $5HT_{2c}$ receptor antagonist drugs have exhibited a strong ability in treating Parkinson's disease [Fox S.H., and Brotchie J.M., A role for 5-HT_{2c} receptor antagonists in the treatment of Parkinson's disease?, *Drug News Perspect*, **12** (8), 477-483 (1999)] while α_2 antagonist compounds are known for their effects on cognitive disorders [Smith A.P. et al., The effects and after effects of the α_2-adrenoceptor antagonist idazoxan on mood, memory and attention in normal volunteers, *J. Psychopharmacol.*, **6** (3), 376-381 (1992)].

no synonyms w. treatment of any kind Cognitive disorder

In the field of depression, it is known for one skilled in the art that mirtazepine as mianserin, play an α_2-adrenoceptor antagonist role [Millan M.J. et al., Mirtazepine enhances frontocortical dopaminergic and corticolimbic adrenergic, but not serotonergic, transmission by blockade of α_2-adrenergic and $serotonin_{2c}$ receptors: a comparison with citalopram, *Eur. J. Neurosci.*, **12**, 1079-95 (2000); De Boer T.H. et al., Differences in modulation of noradrenergic and serotonergic transmission by α_2-adrenoceptor antagonists, mirtazapine, mianserin and idazoxan, *J. Pharmacol. Exp. Ther.*, **277** (2), 852-60 (1997); Haddjeri N. et al., Effects of long-term treatment with the α_2-adrenoceptor antagonist mirtazapine on 5-HT neurotransmission, *Naunyn-Schmiedeberg's Archiv. Pharmacol.*, **355** (1), 20-9 (1997)].

In the end, α_2 and 5-HT_{2c} receptor antagonist drugs can also treat, among other nervous diseases, schizophrenia [for α_2 receptor antagonist drugs

see: Nutt D.J., Putting the 'A' in atypical: does α_2-adrenoceptor antagonism account for the therapeutic advantage of new antipsychotics?, *J. Psychopharmacol.*, **8** (4), 193-195 (1994); Lindstrom L.H., Schizophrenia, the dopamine hypothesis and α_2-adrenoceptor antagonists, *Trends Pharmacol. Sci.*, **21** (6), 198-199 (2000); Millan M.J. et al., S18327 (1-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperid-1-yl]ethyl}3-phenylimidazolin-2-one, a novel, potential antipsychotic displaying marked antagonist properties at α_1- and α_2-adrenergic receptors: II. Functional profile and a multiparametric comparison with haloperidol, clozapine, and 11 other antipsychotic agents, *J. Pharmacol. Exp. Ther.*, **292** (1), 54-66 (2000); and for 5-HT_{2c} receptor antagonist drugs see: Cussac D. et al., Antagonist properties of the novel antipsychotic, S16924, at cloned, human serotonin 5-HT_{2c} receptors: a parallel phosphatidylinosotol and calcium accumulation comparaison with clozapine and haloperidol, *Naunyn-Schmiedeberg's Arch. Pharmacol*, **361** (2), 549-54 (2000); Reavill C et al., Attenuation of haloperidol-induced catalepsy by 5-HT_{2c} receptor antagonist, *Br. J. Pharmacol.*, **126** (3), 572-574 (1999); Gobert A. et al., Serotonin$_{2c}$ receptors tonically suppress the activity of mesocortical dopaminergic and adrenergic, but not serotonergic, pathways: a combined dialysis and electrophysiological analysis in the rat, *Synapse*, **36** (3), 205-221 (2000)] and sexual dysfunction [Lane R.M., A critical review of selective serotonin reuptake inhibitor-related sexual dysfunction; incidence, possible aetiology and implications for management, *J. Psychopharmacol.*, **11** (1), 72-82 (1997)]

Thus, taking into account both enlightenments: publications enclosed connected with "*Pharmacological study*" (pages 38-40) presented in Examples A-D, and "*Background of the invention*" (page 1, line 8 to page 2, line 17) of the present application, we can assume that compounds of US Serial n° 09/896,278 are usable in the treatment of depression, anxiety, schizophrenia, Parkinson's disease, cognitive disorders, libido disorders and sexual dysfunction, sleep disorders, drug abuse and impulsive behaviour disorders.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of the title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth not

MARK MILLAN

Executed at : Courbevoie 18.12.2002

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